Risk of Ischemic Cerebrovascular and Coronary Events in Adult Users of Anticonvulsant Medications in Routine Care Settings

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Background—Older-generation anticonvulsants that highly induce cytochrome P450 enzyme system activity produce metabolic abnormalities that may increase cardiovascular risk. The objective of this study was to evaluate the risk of ischemic cerebrovascular and coronary events in adult new users of anticonvulsants that highly induce cytochrome P450 activity compared with other anticonvulsant agents, as observed in a routine care setting.

Methods and Results—This was a cohort study of patients 40 to 64 years old from the HealthCore Integrated Research Database who had initiated an anticonvulsant medication between 2001 and 2006 and had no recorded major coronary or cerebrovascular condition in the 6 months before treatment initiation. Propensity score (PS) matching was used to evaluate ischemic cerebrovascular and coronary risk among anticonvulsant new users. High-dimensional propensity score (hdPS)–matched analyses were used to confirm adjusted findings. The study identified 913 events in 166 031 unmatched new treatment episodes with anticonvulsant drugs. In a PS-matched population of 22 864 treatment episodes, the rate ratio (RR) for ischemic coronary or cerebrovascular events associated with highly inducing agents versus other agents was 1.22 (95% CI, 0.90-1.65). The RR moved to 0.99 (95% CI, 0.73-1.33) with adjustment for hdPS matching (RR, 1.47; 95% CI, 0.95-2.28 for cerebrovascular events; RR, 0.70; 95% CI, 0.47-1.05 for coronary events).

Conclusions—In this exploratory analysis, there was no evidence of a consistent and statistically significant effect of initiating anticonvulsants that highly induce cytochrome P450 activity on ischemic coronary or cerebrovascular outcomes compared with other agents, given routine care utilization patterns. **(*J Am Heart Assoc.* 2013;2:e000208 doi: 10.1161/JAHA.113.000208)**

Key Words: anticonvulsant drugs • claims data • cohort study • myocardial infarction • stroke

Anticonvulsant medications represent first-line therapy for patients with epilepsy or convulsions, but their use is not limited to the control of seizures. Labeled indications include bipolar disorder, neuropathic pain, and migraine prophylaxis, and considerable off-label use has been reported.[1,2] Given the heterogeneous prescribing patterns and varied benefits of anticonvulsant drugs, a clarification of their safety profile merits attention.

Several investigations have highlighted possible interactions between anticonvulsant drugs and the cardiovascular system. Some of the older anticonvulsants (ie, carbamazepine, phenobarbital, phenytoin, and primidone) have been associated with metabolic changes that may contribute to cardiovascular risk. The mechanism underlying this association might reside in the interaction between these medications and cytochrome P450 system activity.[3] Previous investigations have shown that patients treated with anticonvulsants that highly induce cytochrome P450 enzyme system activity, such as phenytoin, carbamazepine, or phenobarbital, experienced elevated levels of total cholesterol and most of the various lipid fractions, including low-density lipoprotein (LDL) cholesterol and serum triglycerides,[3–5] as well as increases in serum lipoprotein(a) (Lp[a]) and serum homocysteine.[6–9] Meaningful increases in total cholesterol, LDL cholesterol, triglycerides, and Lp(a) have been observed after 2 to 3 months of therapy with carbamazepine,[6,10] and a recent study found that switching from carbamazepine and phenytoin to anticonvulsants not inducing cytochrome P450

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enzyme system activity, such as lamotrigine and levetiracetam, decreased levels of serum cholesterol and C-reactive protein after 6 weeks.[3] Studies have directly quantified atherosclerotic changes associated with long-term therapy with anticonvulsants[11] and have shown that carotid artery intima-media thickness, a strong predictor for future vascular events, appears to be positively correlated with the duration of conventional anticonvulsant therapy.[12]

In the current study we sought to evaluate the risk of cardiovascular events associated with anticonvulsants that highly induce cytochrome P450 activity compared with other anticonvulsant agents as observed in routine care settings among adult anticonvulsant new users. We also investigated the risk of cardiovascular events associated with individual anticonvulsant medications compared with a referent agent.

Methods

Study Population and Data Source

We conducted a cohort study of all subjects aged 40 to 64 years who filled a new prescription for an anticonvulsant agent between July 1, 2001, and December 31, 2006 (index date), and who had 6 months of continuous health plan enrollment without use of any anticonvulsant preceding the index date. Patients became members of the study cohort on the day following the drug initiation. Exclusion criteria were previously defined (Figure 1).[13] Patients were also excluded if they had experienced any ICD-9 diagnosis[14] of the following events in the 6 months prior to the index date: acute myocardial infarction, unstable angina, previous cardiac procedures, and acute ischemic stroke (Table 1). The analysis was restricted to new users of the study drugs to facilitate the assessment of how hazards vary over time and to help define the relationship between duration of use and level of risk.

Medical and pharmacy data were collected from the HealthCore Integrated Research Database, which contains longitudinal healthcare claims data from commercial health plans in the southeastern, mid-Atlantic, central, and western regions of the United States. Data on medical care, prescription drug use, and healthcare utilization are accessible for each subject in the database. For this study, data were available beginning in 2001 for 3 US states (Delaware, Georgia, California), with data from 11 additional states (Virginia, New York, New Jersey, Indiana, Kentucky, Missouri, Ohio, Wisconsin, Connecticut, Maine, New Hampshire) beginning in 2004. Information on the exact date and cause of death was available for the entire study period through linking with the National Death Index (NDI).

Personal identifiers were removed from the data set before the analysis to protect subject confidentiality. The study was approved by the institutional review board of Brigham and Women's Hospital.

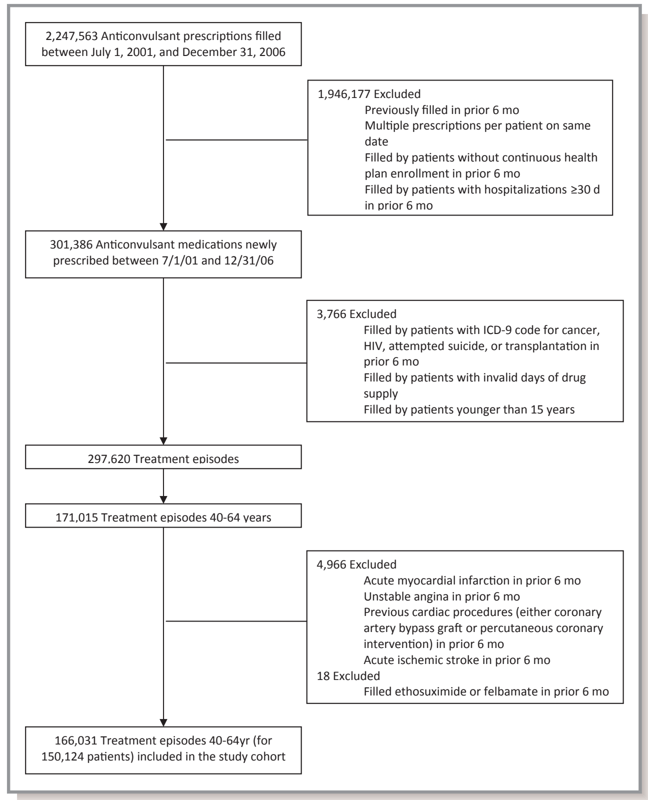


Figure 1. Flowchart of study cohort.

Anticonvulsant Medication Exposure

For study purposes, anticonvulsants were grouped into 2 categories: anticonvulsants that highly induce cytochrome P450 enzyme system activity (ie, carbamazepine, phenobarbital, phenytoin, and primidone) and other anticonvulsants, which included either those minimally inducing (ie, lamotrigine, oxcarbazepine, and topiramate) or those not inducing (ie, gabapentin, levetiracetam, pregabalin, tiagabine, valproate, and zonisamide) cytochrome P450 activity. Valproate, an inhibitor of cytochrome P450 activity, was included among the noninducing agents.[15,16]

For our primary analysis, exposed participants were initiators of any highly inducing anticonvulsant; unexposed participants were initiators of any other anticonvulsant. To investigate the risk associated with individual anticonvulsants, we chose gabapentin and topiramate as our references; both are not highly inducing agents that were among the most widely used in our population during the study period and are characterized by a wide range of indications.

Based on the medication prescribed on the index date, each subject was identified as a new user of a specific anticonvulsant category or agent. Follow-up began on the day following the initial fill. Patients were allowed to have gaps of

Table 1. Population Exclusion Criteria and Study Outcomes

Diagnosis/Procedure	ICD-9CM	ICD-10CM	CPT-4	Comments
Exclusion Criteria				
Acute myocardial infarction	410.xx			
Unstable angina/acute coronary syndrome	411.xx			
Previous cardiac procedure (CABG+PCI)	00.66, 36.01, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.09, 36.1x, 36.2x		33510 to 33536, 33545, 33572, 92973, 92980, 92981, 92982, 92984, 92995, 92996	
Ischemic stroke	433.xx, 434.xx			
Outcomes				
Myocardial infarction	410.xy as primary or secondary, y≠23-day stay required (unless patient died)[17]			
Acute coronary syndrome	411.xx as primary or secondary, 3-day stay required (unless patient died)[18]			
Cardiac procedure (CABG+PCI)	00.66, 36.01, 36.02, 36.03, 36.04, 36.05, 36.06, 36.07, 36.09, 36.1x, 36.2x[18]		33510 to 33536, 33545, 33572, 92973, 92980, 92981, 92982, 92984, 92995, 92996	
Ischemic stroke, without transient ischemic attack (TIA)	433.x1, 434.x1, 436.xx, 437.1x, or 437.9x[19]			
Death for ischemic heart disease		I20.xx to I25.xx		NDI primary cause of death
Cerebrovascular ischemic death		I63.xx to I66.xx, I67.2x, I67.8x, 167.9x		NDI primary cause of death

CPT-4, Current Procedural Terminology-4 codes; NDI, National Death Index; ICD, International Classification of Diseases; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

up to 30 days between prescription fill dates in the calculation of continuous therapy. In the case of drug discontinuation, the exposure risk window for each patient treatment episode extended until 30 days after the expiration of the supply of the last prescription. Participants were followed until the end of their exposure risk window, switching to another anticonvulsant agent, the occurrence of a study event (the first event occurring *within each outcome category* investigated), death from causes not included in the study outcome, end of continuous health plan enrollment, or the end of the study period, whichever came first (as-treated analysis). Patients were allowed to contribute >1 treatment episode if they had a 6-month washout period without filling any study drug. In an alternative approach, assuming that any cardiovascular event shortly after treatment start is unlikely to be treatment emergent based on a metabolic hypothesis, we required a 3-month induction period between the initial fill and the beginning of the follow-up time, limiting the analysis to only those patients who were still receiving therapy at 3 months. Finally, to assess the impact of duration on anticonvulsant therapy, we further limited the analysis to patients who were continuously on therapy at 6 and 9 months, so follow-up started 6 and 9 months, respectively, after the first prescription was filled.

Outcomes

The primary study outcome was a composite of ischemic coronary events (hospitalization for myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, or death from ischemic heart disease) and ischemic cerebrovascular events (ischemic stroke or ischemic cerebrovascular death). For myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, and ischemic stroke, we used previously validated claims algorithms[17–19] (Table 1). Ischemic cerebrovascular and coronary events were also investigated as 2 separate outcome categories.

Causes of death were determined through NDI linkage. Deaths from ischemic heart disease were identified through recorded ICD-10 codes (I20-I25), whereas cerebrovascular ischemic deaths were identified as I63-I66, I67.2, I67.8, or I67.9.[20] Only primary causes of death were considered.

Within each outcome category investigated, only the first event was considered. Patients were censored at this point including any subsequent treatment episode(s).

Patient Characteristics

Patient characteristics were identified during the 6 months preceding cohort entry and included age, sex, calendar year, healthcare utilization, and comorbidities investigated via ICD-9 codes and Current Procedural Terminology–4 (CPT-4) codes.[21] These comorbidities included old myocardial infarction, stable angina, other ischemic heart diseases, hypertension, heart failure, arrhythmias, diabetes mellitus, transient ischemic attack, other evidence of cerebrovascular disease (cerebral hemorrhagic events, cerebrovascular procedure), other cardiovascular conditions (eg, valvular disease, aneurysm, or peripheral vascular disease), epilepsy and seizure disorders, migraine, neuropathic pain, mood disorders, psychotic disorders, dementia, and other psychiatric disorders. Healthcare utilization included prior hospitalizations, physician visits, use of other cardiovascular and psychotropic medications, and number of distinct medications used.

Statistical Analysis

Characteristics of the patients were cross-tabulated by their use of anticonvulsant agents. For each exposure, the number of treatment episodes, number of events, and incidence rates for cardiovascular and cerebrovascular events were calculated until the date of censoring.

To control for confounding by indication, we constructed an exposure propensity score from the subjects' baseline covariates (Table 2).[22] Distinct propensity scores were estimated for each comparison. Exposure groups were 1:1 matched on their propensity score (PS) using a "greedy" matching algorithm[23] with a maximum caliper of 0.01. Absolute standardized differences, that is, the difference in means or proportions divided by the pooled standard deviation, were used to compare covariates' mean or prevalence within exposure groups before and after PS matching.[24] After PS matching, incidence rates, rate ratios (RRs), and rate differences (RDs), with 95% confidence intervals (CIs), were calculated for each matched cohort for all outcomes. To further improve covariate balance, we also used high-dimensional propensity score (hdPS) matching, which augmented the standard PS matching with 500 additional empirically identified covariates. The hdPS algorithm is an automated technique that examines thousands of candidate covariates among different claims data dimensions in the study population, for example, dispensed drugs, recorded diagnoses, and performed procedures, and empirically prioritizes 500 potential confounders for matching (the detailed list of the 500 empirical covariates included in the main analysis is provided in the Supplemental Material). Some empirical studies have shown that the hdPS algorithm may improve adjustment for confounding.[25,26] Finally, to evaluate whether the effect of highly inducing anticonvulsants versus other anticonvulsants varied over time, we tested the proportional hazards assumption by including an interaction term between time and exposure in Cox proportional hazards regression models.

Sensitivity analyses were performed to test the robustness of the primary findings. First, we extended the exposure risk window until 90 days after the expiration of the supply of the last prescription, assuming that the atherogenic effect of anticonvulsant therapy might persist longer after treatment discontinuation. Second, mimicking an intention-to-treat analysis, the initial exposure to a specific anticonvulsant category or an individual agent was carried forward until the end of a fixed 2-year follow-up period.

Adjustments for multiple comparisons were not considered. In this exploratory analysis, we limited analyses to estimation of effects and precision rather than any formal statistical testing.[27,28]

Results

We identified 166 031 new treatment episodes for 150 124 patients (Figure 1). Among those, 12 580 were new users of highly inducing anticonvulsants and 153 451 were initiators of other anticonvulsants. Compared with new users of other agents, new users of highly inducing anticonvulsants were more likely to be male, to have more frequent prior hospitalizations, and to have a history of cardiac arrhythmia, other cardiovascular diseases, hemorrhagic stroke, and epilepsy (Table 2). Those patients visited a physician less frequently, and were less likely to have a history of diabetes and hyperlipidemia and to have received antihypertensives, lipid-lowering agents, insulin, and oral hypoglycemics in the 6 months prior to anticonvulsant treatment initiation. These covariates appeared to be balanced after PS matching. Within the individual anticonvulsant medications, patients who were gabapentin initiators were more likely to have a history of stable angina or other ischemic coronary diseases and patients with diabetes to have received antihypertensive drugs, lipid-lowering agents, insulin, and oral hypoglycemic drugs, whereas patients beginning topiramate were generally younger and more likely to be female, to have a history of migraine, and to have had fewer hospitalizations (Table 3). The overall mean follow-up was 4.1 (5.4) months and was compatible between exposure groups (4.6 and 4.1 months for highly inducing anticonvulsants and other anticonvulsant

Table 2. Patient Characteristics by Drug Exposure in Original and PS-matched Populations for Highly Enzyme-Inducing Anticonvulsants Versus Other Anticonvulsants*†

	Highly Inducing Anticonvulsants (ACs)	Other ACs	Absolute Standardized Difference‡	Highly Inducing ACs *After PS Matching*	Other ACs *After PS Matching*	Absolute Standardized Difference *After PS Matching*
Observations, No.	n=12 580	n=15 3451		n=11 432	n=11 432	
Age, y, mean (SD)	51.4 (7.0)	50.9 (6.8)	0.1	51.4 (7.0)	51.4 (7.0)	0.0
Female	6750 (53.7)	99969 (65.2)	0.2	6386 (55.9)	6378 (55.8)	0.0
Charlson index, score=0	9462 (75.2)	118365 (77.1)	0.0	8819 (77.1)	8812 (77.1)	0.0
Charlson index, score=1	1991 (15.8)	24536 (16.0)	0.0	1697 (14.8)	1736 (15.2)	0.0
Charlson index, score ≥2	1127 (9.0)	10550 (6.9)	0.1	916 (8.0)	884 (7.7)	0.0
N drugs, mean (SD)	5.7 (5.0)	7.4 (5.3)	0.3	5.9 (5.0)	5.9 (5.0)	0.0
Prior hospitalization	2783 (22.1)	18237 (11.9)	0.3	2126 (18.6)	2020 (17.7)	0.0
N visits, mean (SD)	2.9 (3.8)	4.2 (4.4)	0.3	3.1 (3.9)	3.2 (3.9)	0.0
Prior cardiovascular hospitalization	1374 (10.9)	6504 (4.2)	0.3	956 (8.4)	886 (7.8)	0.0
History of myocardial infarction	39 (0.3)	382 (0.3)	0.0	33 (0.3)	43 (0.4)	0.0
Stable angina and other ischemic coronary diseases	412 (3.3)	5310 (3.5)	0.0	372 (3.3)	380 (3.3)	0.0
Hypertension	2233 (17.8)	27659 (18.0)	0.0	1987 (17.4)	2007 (17.6)	0.0
Heart failure	137 (1.1)	1489 (1.0)	0.0	115 (1.0)	117 (1.0)	0.0
Cardiac arrhythmia	520 (4.1)	4399 (2.9)	0.1	409 (3.6)	442 (3.9)	0.0
Other cardiovascular diseases	418 (3.3)	3806 (2.5)	0.0	348 (3.0)	339 (3.0)	0.0
Hemorrhagic stroke	487 (3.9)	292 (0.2)	0.3	286 (2.5)	212 (1.9)	0.0
Transient ischemic attack (TIA)	177 (1.4)	984 (0.6)	0.1	131 (1.1)	160 (1.4)	0.0
Other ischemic cerebrovascular disease	393 (3.1)	1587 (1.0)	0.1	288 (2.5)	288 (2.5)	0.0
Diabetes	1206 (9.6)	22278 (14.5)	0.2	1136 (9.9)	1231 (10.8)	0.0
Hyperlipidemia	911 (7.2)	13132 (8.6)	0.1	846 (7.4)	923 (8.1)	0.0
Peripheral vascular disease	140 (1.1)	719 (0.5)	0.1	111 (1.0)	88 (0.8)	0.0
Seizure disorder	2978 (23.7)	2802 (1.8)	0.7	1950 (17.1)	2052 (17.9)	0.0
Depression	1280 (10.2)	22692 (14.8)	0.1	1212 (10.6)	1166 (10.2)	0.0
Bipolar disorder	322 (2.6)	6912 (4.5)	0.1	319 (2.8)	359 (3.1)	0.0
Migraine	516 (4.1)	16358 (10.7)	0.3	506 (4.4)	552 (4.8)	0.0
Psychotic disorders	207 (1.7)	1419 (0.9)	0.1	159 (1.4)	199 (1.7)	0.0
Dementia	217 (1.7)	688 (0.5)	0.1	159 (1.4)	169 (1.5)	0.0
Alcohol/drug abuse	1125 (8.9)	7142 (4.7)	0.2	873 (7.6)	851 (7.4)	0.0
Any antihypertensive drug§	4606 (36.6)	60321 (39.3)	0.1	4250 (37.2)	4340 (38.0)	0.0
Lipid-lowering agents	2254 (17.9)	33108 (21.6)	0.1	2140 (18.7)	2148 (18.8)	0.0
Insulin	287 (2.3)	5521 (3.6)	0.1	272 (2.4)	292 (2.6)	0.0
Oral hypoglycemics	834 (6.6)	16023 (10.4)	0.1	790 (6.9)	861 (7.5)	0.0
Anticoagulants (heparin or warfarin)	203 (1.6)	2607 (1.7)	0.0	190 (1.7)	188 (1.6)	0.0
Platelet-aggregation inhibitors‖	278 (2.2)	2893 (1.9)	0.0	248 (2.2)	220 (1.9)	0.0
Antiarrhythmic agents	58 (0.5)	524 (0.3)	0.0	52 (0.5)	44 (0.4)	0.0

Continued

Table 2. Continued

	Highly Inducing Anticonvulsants (ACs)	Other ACs	Absolute Standardized Difference‡	Highly Inducing ACs *After PS Matching*	Other ACs *After PS Matching*	Absolute Standardized Difference *After PS Matching*
Observations, No.	n=12 580	n=15 3451		n=11 432	n=11 432	
Antidepressant agents	3761 (29.9)	72057 (47.0)	0.4	3631 (31.8)	3583 (31.3)	0.0
Antipsychotic agents	717 (5.7)	11115 (7.2)	0.1	682 (6.0)	717 (6.3)	0.0

SD indicates standard deviation; PS, propensity score; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
*The propensity scores were based on all the variables in Table 1 and calendar year.
†Six months prior to index date.
‡Absolute standardized difference was defined as the difference in means divided by the pooled standard deviation.[26]
§Includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, calcium channel blockers, or other antihypertensives.
‖Includes clopidogrel, dipyridamole, aspirin/dipyridamole, or ticlopidine.

agents in the unmatched population, 4.4 and 4.2 months in the PS-matched populations, respectively). Anticonvulsant discontinuation (71.9%) and end of continuous plan enrollment (18.5%) were the most common reasons for censoring.

During the follow-up period, we identified 913 ischemic coronary or cerebrovascular events (611 coronary events and 328 cerebrovascular events), resulting in an event rate of 16.2 events per 1000 person-years (95% CI, 15.2-17.3). In a PS-matched analysis, highly inducing anticonvulsants were associated with a not statistically significant increased risk of ischemic coronary or cerebrovascular events compared with the other anticonvulsant agents (RR, 1.22; 95% CI, 0.90-1.65; Table 4). This effect was attenuated to 1.13 (95% CI, 0.70-1.82) after accounting for a 3-month induction period. With adjustment for 1:1 hdPS-matching, the RR moved to 0.99 (95% CI, 0.73-1.33), and to 0.95 (95% CI, 0.59-1.52) after accounting for a 3-month induction period. However, when the 2 outcome categories were considered separately, the hdPS analysis suggested a nonsignificant increased risk of ischemic cerebrovascular events when highly inducing anticonvulsants were compared with the other anticonvulsant agents (RR, 1.48; 95% CI, 0.70-3.13). There was no indication of increased risk for coronary events (RR, 0.75; 95% CI, 0.41-1.36). When duration on treatment was considered, the analysis suggested a possible pattern of increasing hazard ratios for ischemic cerebrovascular events and for total cardiovascular risk (Table 5). However, the test for proportionality was not statistically significant for any of the 3 outcomes ($P>0.05$), which indicates that the effect of highly inducing anticonvulsants versus other anticonvulsants was not statistically different over time.

HdPS adjusted cumulative distribution function plots were consistent with our findings (Figures 2–4).

The intention-to-treat-type analyses carrying forward the first exposure yielded results similar to the primary "as-treated" analysis (Table 6). Similarly, there was no meaningful difference when we extended the exposure risk window until 90 days after drug discontinuation (Table 7).

In 1:1 hdPS-matched analyses of individual anticonvulsants, carbamazepine, primidone, oxcarbazepine, gabapentin, and pregabalin initiators showed increased cardiovascular risk when compared with topiramate (Figure 5). When compared with gabapentin, the risk for these agents remained elevated but became statistically nonsignificant. After accounting for a 3-month induction period, only carbamazepine and gabapentin initiators appeared to have a statistically significant increased risk of cardiovascular events compared with topiramate, with an RR of 3.51 (95% CI, 1.13-10.88) and an RR of 2.06 (95% CI, 1.21-3.50), respectively. Carbamazepine initiators consistently showed increased but not statistically significant risk when compared with gabapentin (RR, 2.0; 95% CI, 0.82-4.91). The small subgroup sizes of individual anticonvulsant agents did not allow for a conclusive investigation of the separated outcomes.

Discussion

Anticonvulsant medications are widely prescribed for several medical conditions, but little is known about their cardiovascular safety. We evaluated ischemic cerebrovascular and coronary risk in PS and hdPS–matched cohorts based on 166 031 anticonvulsant treatment episodes and 913 coronary or cerebrovascular events.

We found no evidence of any consistent and meaningful increase in the relative risk of ischemic coronary or cerebrovascular events associated with the use of anticonvulsants that highly induce cytochrome P450 activity compared with other agents during the study follow-up. However, we found a not statistically significant increase in the relative risk of noticeable magnitude for cerebrovascular events, which became more marked, although less precise, with duration on treatment. In an evaluation of individual anticonvulsant agents, the risk of ischemic coronary or cerebrovascular events appeared to be consistently increased for initiators of carbamazepine compared with topiramate or gabapentin.

Table 3. Selected Patient Characteristics by Single Drug Exposure

	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Primidone	Tiagabine	Topiramate	Valproate	Zonisamide
N Obs	5102	90555	9663	1858	3383	1076	4806	5456	1596	3244	30089	7255	1948
Age, y (SD)	51.0 (6.9)	51.8 (6.8)	49.4 (6.4)	50.5 (6.7)	49.6 (6.7)	50.5 (6.8)	51.1 (6.9)	52.7 (6.8)	54.3 (6.8)	50.1 (6.4)	49.1 (6.3)	49.4 (6.6)	49.9 (6.5)
Female	3136 (61.5)	55331 (61.1)	6079 (62.9)	1148 (61.8)	2078 (61.4)	625 (58.1)	2161 (45.0)	3240 (59.4)	828 (51.9)	2005 (61.8)	24471 (81.3)	4198 (57.9)	1419 (72.8)
Charlson index (SD)	0.2 (0.6)	0.4 (0.8)	0.2 (0.5)	0.5 (1.1)	0.3 (0.6)	0.3 (0.7)	0.7 (1.6)	0.5 (0.9)	0.3 (0.7)	0.3 (0.7)	0.2 (0.6)	0.3 (0.7)	0.3 (0.6)
N drugs (SD)	5.8 (4.9)	7.5 (5.3)	6.8 (5.1)	6.7 (5.6)	6.5 (5.3)	5.8 (5.5)	5.3 (4.7)	8.2 (6.1)	6.6 (5.3)	8.0 (5.8)	7.3 (5.3)	6.6 (5.2)	6.9 (5.8)
Prior hospitalization	545 (10.7)	11532 (12.7)	1075 (11.1)	434 (23.4)	515 (15.2)	211 (19.6)	1921 (40.0)	631 (11.6)	106 (6.6)	411 (12.7)	2136 (7.1)	1313 (18.1)	190 (9.8)
N Visits (SD)	3.1 (3.7)	4.3 (4.4)	3.0 (3.8)	4.6 (4.4)	3.7 (4.2)	3.3 (5.1)	2.4 (3.4)	4.7 (4.9)	3.9 (3.9)	5.0 (4.7)	4.1 (4.1)	3.0 (4.0)	4.9 (4.4)
History of myocardial infarction	10 (0.2)	299 (0.3)	11 (0.1)	3 (0.2)	7 (0.2)	2 (0.2)	20 (0.4)	9 (0.2)	7 (0.4)	4 (0.1)	32 (0.1)	14 (0.2)	3 (0.2)
Stable angina and other ischemic diseases	141 (2.8)	3629 (4.0)	242 (2.5)	66 (3.6)	92 (2.7)	35 (3.3)	172 (3.6)	256 (4.7)	64 (4.0)	111 (3.4)	655 (2.2)	205 (2.8)	54 (2.8)
Hypertension	795 (15.6)	17871 (19.7)	1195 (12.4)	330 (17.8)	486 (14.4)	178 (16.5)	905 (18.8)	1061 (19.5)	355 (22.2)	596 (18.4)	4807 (16.0)	972 (13.4)	341 (17.5)
Congestive heart failure	25 (0.5)	1051 (1.2)	34 (0.4)	26 (1.4)	28 (0.8)	5 (0.5)	89 (1.6)	60 (1.1)	18 (1.1)	30 (0.9)	182 (0.6)	64 (0.9)	14 (0.7)
Cardiac arrhythmia	114 (2.2)	2792 (3.1)	252 (2.6)	98 (5.3)	101 (3.0)	20 (1.9)	315 (6.6)	165 (3.0)	71 (4.5)	90 (2.8)	635 (2.1)	206 (2.8)	60 (3.1)
Other cardiovascular diseases	107 (2.1)	2613 (2.9)	133 (1.4)	74 (4.0)	61 (1.8)	18 (1.7)	248 (5.2)	163 (3.0)	45 (2.8)	65 (2.0)	531 (1.8)	112 (1.5)	54 (2.8)
Hemorrhagic stroke	25 (0.5)	127 (0.1)	7 (0.1)	74 (4.0)	6 (0.2)	8 (0.7)	451 (9.4)	4 (0.1)	3 (0.2)	4 (0.1)	43 (0.1)	24 (0.3)	3 (0.2)
TIA	46 (0.9)	488 (0.5)	42 (0.4)	56 (3.0)	39 (1.2)	3 (0.3)	111 (2.3)	32 (0.6)	17 (1.1)	5 (0.2)	246 (0.8)	59 (0.8)	17 (0.9)
Other ischemic CBV disease	61 (1.2)	857 (1.0)	62 (0.6)	100 (5.4)	56 (1.7)	10 (0.9)	303 (6.3)	63 (1.2)	19 (1.2)	31 (1.0)	314 (1.0)	80 (1.1)	24 (1.2)
Diabetes	488 (9.6)	15913 (17.6)	734 (7.6)	155 (8.3)	282 (8.3)	65 (6.0)	459 (9.6)	1335 (24.5)	194 (12.2)	277 (8.5)	2753 (9.2)	619 (8.5)	210 (10.8)
Hyperlipidemia	355 (7.0)	8114 (9.0)	707 (7.3)	143 (7.7)	275 (8.1)	79 (7.3)	327 (6.8)	522 (9.6)	150 (9.4)	251 (7.7)	2499 (8.3)	460 (6.3)	161 (8.3)
Peripheral vascular disease	15 (0.3)	573 (0.6)	11 (0.1)	25 (1.4)	10 (0.3)	5 (0.5)	115 (2.4)	23 (0.4)	5 (0.3)	8 (0.3)	44 (0.2)	20 (0.3)	5 (0.3)
Epilepsy	559 (11.0)	531 (0.6)	326 (3.4)	535 (28.8)	355 (10.5)	134 (12.5)	2238 (46.6)	45 (0.8)	47 (2.9)	42 (1.3)	499 (1.7)	379 (5.2)	90 (4.6)

Continued

Table 3. Continued

	Carbamazepine	Gabapentin	Lamotrigine	Levetiracetam	Oxcarbazepine	Phenobarbital	Phenytoin	Pregabalin	Primidone	Tiagabine	Topiramate	Valproate	Zonisamide
Depression	600 (11.8)	9182 (10.1)	3958 (41.0)	226 (12.2)	920 (27.2)	148 (13.8)	377 (7.8)	488 (8.9)	155 (9.7)	871 (26.9)	4812 (16.0)	1917 (26.4)	318 (16.3)
Bipolar disorder	261 (5.1)	972 (1.1)	2566 (26.6)	30 (1.6)	610 (18.0)	11 (1.0)	33 (0.7)	57 (1.0)	17 (1.1)	145 (4.5)	942 (3.1)	1524 (21.0)	66 (3.4)
Migraine	234 (4.6)	3605 (4.0)	445 (4.6)	312 (16.8)	176 (5.2)	66 (6.1)	172 (3.6)	219 (4.0)	44 (2.8)	204 (6.3)	9962 (33.1)	1008 (13.9)	427 (21.9)
Neuropathic pain	1263 (24.8)	23323 (25.8)	801 (8.3)	317 (17.1)	635 (18.8)	86 (8.0)	286 (6.0)	1736 (31.8)	188 (11.8)	756 (23.3)	3780 (12.6)	537 (7.4)	411 (21.1)
Psychotic disorders	57 (1.1)	373 (0.4)	233 (2.4)	43 (2.3)	113 (3.3)	16 (1.5)	121 (2.5)	22 (0.4)	13 (0.8)	38 (1.2)	208 (0.7)	381 (5.3)	8 (0.4)
Dementia	43 (0.8)	287 (0.3)	50 (0.5)	46 (2.5)	35 (1.0)	8 (0.7)	143 (3.0)	9 (0.2)	23 (1.4)	17 (0.5)	110 (0.4)	124 (1.7)	10 (0.5)
Alcohol/drug abuse	280 (5.5)	4030 (4.5)	596 (6.2)	136 (7.3)	278 (8.2)	191 (17.8)	601 (12.5)	184 (3.4)	53 (3.3)	272 (8.4)	976 (3.2)	609 (8.4)	61 (3.1)
Any antihypertensive drug*	1742 (34.1)	37307 (41.2)	2765 (28.6)	703 (37.8)	1048 (31.0)	358 (33.3)	1612 (33.5)	2600 (47.7)	894 (56.0)	1202 (37.1)	11555 (38.4)	2359 (32.5)	782 (40.1)
Lipid-lowering agents	963 (18.9)	21322 (23.6)	1706 (17.7)	328 (17.7)	633 (18.7)	155 (14.4)	731 (15.2)	1663 (30.5)	405 (25.4)	611 (18.8)	5271 (17.5)	1209 (16.7)	365 (18.7)
Insulin	102 (2.0)	4193 (4.6)	124 (1.3)	30 (1.6)	56 (1.7)	14 (1.3)	126 (2.6)	431 (7.9)	45 (2.8)	53 (1.6)	478 (1.6)	116 (1.6)	40 (2.1)
Oral hypoglycemics	366 (7.2)	11603 (12.8)	479 (5.0)	88 (4.7)	189 (5.6)	36 (3.4)	294 (6.1)	965 (17.7)	138 (8.7)	181 (5.6)	1953 (6.5)	408 (5.6)	157 (8.1)
Anticoagulants (heparin or warfarin)	58 (1.1)	1860 (2.1)	72 (0.8)	46 (2.5)	40 (1.2)	20 (1.7)	95 (2.0)	151 (2.8)	30 (1.9)	52 (1.6)	269 (0.9)	88 (1.2)	29 (1.5)
Platelet-aggregation inhibitors†	98 (1.9)	1979 (2.2)	104 (1.1)	56 (3.0)	45 (1.3)	16 (1.5)	131 (2.7)	205 (3.8)	33 (2.1)	43 (1.3)	321 (1.1)	111 (1.5)	29 (1.5)

SD indicates standard deviation; TIA, transient ischemic attack; CHF, congestive heart failure; CBV, cerebrovascular.
*Includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, calcium channel blockers, or other antihypertensives.
†Includes clopidogrel, dypridamole, aspirin/dypridamole, or ticlopidine.

Table 4. Incidence Rates (IRs), Rate Ratios (RRs), and Rate Differences (RDs) for Study Outcomes in Unadjusted, PS-, and hdPS-Matched Population—As-Treated Analysis*

Follow-up	Follow-up Starts on Day 1			Follow-up Starts on Day 90		
Adjustment	Unadjusted Analysis	1:1 PS Matching	1:1 HdPS Matching	Unadjusted Analysis	1:1 PS Matching	1:1 HdPS Matching
N episodes	166 031	22 864†	22 190†	57 433	7686	7572
Ischemic Coronary‡ or Cerebrovascular§ Events						
No. of events (IRs per 1000 person-years)						
Highly enzyme-inducing ACs	112 (23.7)	94 (23.0)	87 (21.8)	44 (17.9)	38 (18.7)	36 (18.0)
Other ACs	801 (15.5)	74 (18.8)	85 (22.0)	305 (13.3)	30 (16.5)	34 (18.9)
Highly enzyme-inducing ACs vs.						
Other ACs	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.52 (1.25 to 1.85)	1.22 (0.90 to 1.65)	0.99 (0.73 to 1.33)	1.35 (0.98 to 1.85)	1.13 (0.70 to 1.82)	0.95 (0.59 to 1.52)
RD‖ (95% CI)	8.15 (3.63 to 12.67)	4.21 (−2.10 to 10.52)	−0.18 (−6.73 to 6.37)	4.66 (−0.85 to 10.17)	2.18 (−6.18 to 10.54)	−0.86 (−9.53 to 7.81)
Ischemic Coronary Events						
No. of events (IRs per 1000 person-years)						
Highly enzyme-inducing ACs	45 (9.5)	41 (10.0)	40 (10.0)	23 (9.3)	20 (9.8)	20 (10.0)
Other ACs	566 (11.0)	45 (11.4)	55 (14.2)	219 (9.5)	18 (9.9)	24 (13.3)
Highly enzyme-inducing ACs vs.						
Other ACs	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	0.86 (0.63 to 1.17)	0.88 (0.58 to 1.34)	0.70 (0.47 to 1.05)	0.98 (0.64 to 1.51)	0.99 (0.52 to 1.87)	0.75 (0.41 to 1.36)
RD (95% CI)	−1.49 (−4.40 to 1.42)	−1.41 (−5.93 to 3.11)	−4.20 (−9.06 to 0.66)	−0.19 (−4.20 to 3.82)	−0.11 (−6.36 to 6.14)	−3.33 (−10.21 to 3.55)
Ischemic Cerebrovascular Events						
No. of events (IRs per 1000 person-years)						
Highly enzyme-inducing ACs	70 (14.8)	55 (13.4)	50 (12.5)	23 (9.4)	19 (9.3)	18 (9.0)
Other ACs	258 (5.0)	33 (8.4)	33 (8.5)	97 (4.2)	12 (6.6)	11 (6.1)
Highly enzyme-inducing ACs vs.						
Other ACs	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	2.96 (2.27 to 3.85)	1.61 (1.05 to 2.48)	1.47 (0.95 to 2.28)	2.23 (1.42 to 3.51)	1.42 (0.69 to 2.93)	1.48 (0.70 to 3.13)
RD (95% CI)	9.78 (6.27 to 13.29)	5.07 (0.52 to 9.62)	4.00 (−0.52 to 8.52)	5.15 (1.24 to 9.06)	2.74 (−2.85 to 8.33)	2.91 (−2.58 to 8.40)

PS indicates propensity score; hdPS, high-dimensional propensity score; ACs, anticonvulsants; CI, confidence interval.

*As-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, or the end of the study period, whichever came first.

†Number of successfully matched patients among initiators of highly enzyme-inducing ACs and other ACs.

‡Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, or death for ischemic heart disease.

§Ischemic stroke or ischemic cerebrovascular death.

‖Rate differences are per 1000 person-years.

Table 5. Effect of Duration on Therapy with Highly Enzyme-Inducing Anticonvulsants Versus Other Anticonvulsants on Ischemic Coronary* or Cerebrovascular† Events in hdPS-Matched Population‡

Duration on Anticonvulsant Therapy	Ischemic Coronary or Cerebrovascular Events	Ischemic Coronary Events	Ischemic Cerebrovascular Events
	HR (95%)	HR (95%)	HR (95%)
≥3 Months	0.98 (0.61 to 1.56)	0.77 (0.43 to 1.40)	1.47 (0.70 to 3.13)
≥6 Months	1.45 (0.75 to 2.82)	1.11 (0.48 to 2.53)	2.17 (0.77 to 6.11)
≥9 Months	1.81 (0.82 to 3.98)	1.17 (0.44 to 3.07)	4.81 (1.07 to 21.52)
Test for proportional hazards	*P*=0.38	*P*=0.54	*P*=0.45

hdPS indicates high-dimensional propensity score; HR, hazard ratio.
*Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, or death for ischemic heart disease.
†Ischemic stroke or ischemic cerebrovascular death.
‡As-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, or the end of the study period, whichever came first.

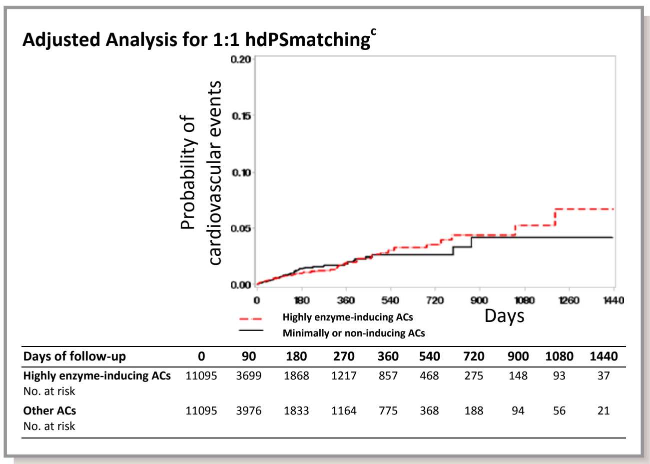


Figure 2. Probability of ischemic coronary or cerebrovascular events[a] by anticonvulsant category and time since treatment initiation.[b] [a]Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, death for ischemic heart disease, ischemic stroke, or ischemic cerebrovascular death. [b]AT, as-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, the end of the study period or end of 1 year, whichever came first. [c]Cumulative probability estimates of ischemic coronary or cerebrovascular events over time were restricted to the hdPS-matched sample. hdPS indicates high-dimensional propensity score; ACs, anticonvulsants.

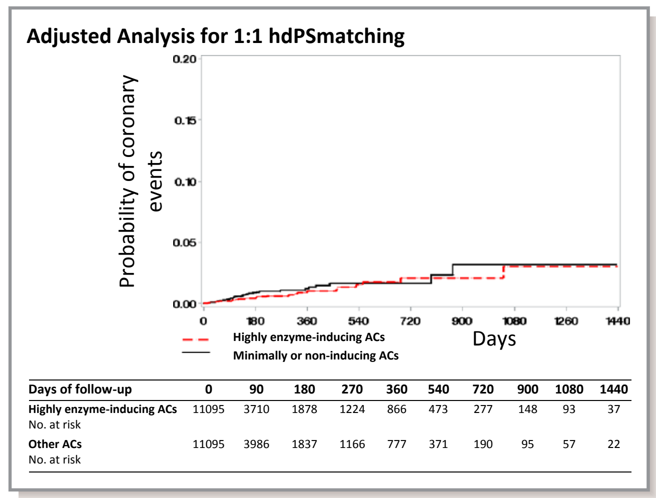


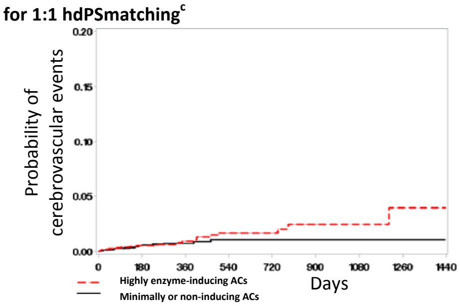
Figure 3. Probability of ischemic coronary events[a] by anticonvulsant category and time since treatment initiation.[b] [a]Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, death for ischemic heart disease. [b]AT, as-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, the end of the study period or end of 1 year, whichever came first. [c]Cumulative probability estimates of ischemic coronary events over time were restricted to the hdPS-matched sample. hdPS indicates high-dimensional propensity score; ACs, anticonvulsants.

However, these latter results should be considered in light of the small subgroup sizes of individual anticonvulsant agents.

These findings are not incompatible with the hypothesis that conventional anticonvulsants with highly inducing cytochrome P450 enzyme system activity increase cardiovascular risk, possibly influencing atherothrombotic risk factors such as serum lipids, lipoprotein(a), homocysteine, and C-reactive protein and carotid artery intima-media thickness and that the risk for cardiovascular events increases with the duration of therapy. Our results of not significantly increased risk for cerebrovascular events but not for coronary events may indicate different baseline risks in the population. Epileptic seizures have been suggested to be the first manifestation of otherwise undiagnosed cerebrovascular disease.[29,30] In such a context, highly inducing anticonvulsants might act as risk promoters and precipitate the occurrence of cerebrovascular events.

Few investigations have directly addressed the relationship between anticonvulsant medications and cardiovascular risk.

Adjusted Analysis for 1:1 hdPSmatching[c]



Days of follow-up	0	90	180	270	360	540	720	900	1080	1440
Highly enzyme-inducing ACs No. at risk	11095	3704	1874	1222	859	471	276	148	94	38
Other ACs No. at risk	11095	3985	1845	1170	780	371	189	95	56	21

Figure 4. Probability of ischemic cerebrovascular events[a] by anticonvulsant category and time since treatment initiation.[b] [a]Ischemic stroke or ischemic cerebrovascular death. [b]AT, as-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, the end of the study period or end of 1 year, whichever came first. [c]Cumulative probability estimates of ischemic cerebrovascular events over time were restricted to the hdPS-matched sample. hdPS indicates high-dimensional propensity score; ACs, anticonvulsants.

Olesen et al[31] found that patients with epilepsy being treated with valproate had a lower risk of myocardial infarction compared with the general population. The same authors performed a cohort study of epileptic patients and found that, compared with carbamazepine, both oxcarbazepine and phenobarbital were associated with increased risk of cardiovascular death and all-cause death, oxcarbazepine with increased risk of stroke, and valproate with a decreased risk of MI and stroke.[32] Both those investigations did not address a direct comparison between highly inducing anticonvulsants and other agents, had different underlying populations, and examined a restricted number of anticonvulsant agents.

Our study exhibits several strengths. Through the use of a large claims-based population, we were able to investigate new users of anticonvulsant drugs in a routine care setting. Initiators of anticonvulsant drugs were compared with initiators of an active referent anticonvulsant category or drug (instead of no treatment) to provide clinicians with useful information regarding the relative treatment risks and benefits. Finally, multiple approaches in the design and analysis of the study were employed to minimize the potential for residual confounding, including the restriction to drug initiators without any major coronary or cerebrovascular events in the 6 months prior to drug initiation, the restriction to patients with at least 3 months of continuous anticonvulsant therapy before follow-up started, and the extensive covariate adjustment via standard PS- and hdPS–matched analyses.

There are limitations to be considered. Some important characteristics might not have been completely captured as either not fully or not directly measured in claims data, for exaple, BMI, smoking, and disease severity. Although multiple approaches in terms of study design and analysis were used, including hdPS methodology, which has been shown to improve adjustment by identifying covariates that may be proxies for unmeasured characteristics,[25,26] residual confounding cannot be completely ruled out. Initiators of noninducing anticonvulsants, in particular gabapentin and pregabalin, more frequently showed characteristics predictive of higher cardiovascular risk. These characteristics, if not fully measured in claims data and accounted for in the adjusted analyses, may have contributed to the finding of not consistent statistically significant increases in the relative risk of ischemic coronary or cerebrovascular events associated with the use of highly inducing anticonvulsants compared with other agents. Furthermore, pregabalin and gabapentin have been associated with peripheral edema and weight gain,[33,34] possibly contributing to heart failure and left ventricular systolic dysfunction.[35] This might have diluted the effect on the cardiovascular system of highly inducing anticonvulsants. A second limitation is that anticonvulsant drug discontinuation or switching might be related to early cardiovascular effects. This could have made discontinuination or switching a predictor for cardiovascular events that would not have been observed in an as-treated analysis, therefore introducing bias toward the null. To minimize this potential bias, we extended the exposure risk window until 30 and 90 days after drug discontinuation, and we also carried the first exposure forward, similar to an intention-to-treat analysis, without considering either drug discontinuation or switching. The results of this analysis were consistent. Another limitation is the high degree of drug discontinuation in our routine care setting, which limited the possibility of investigating the effect of anticonvulsant medications beyond the first 2 years of therapy with sufficient power. This reflects routine care, and the data are consistent with real-world patterns of adherence. Regardless, meaningful metabolic changes have been shown to occur as early as after 2 to 3 months of continuous treatment with highly inducing anticonvulsants.[6,10]

In conclusion, this study explores possible differences in ischemic coronary or cerebrovascular risk among adult anticonvulsant initiators in real-world healthcare settings. There was no evidence of a consistent statistically significant increase in the relative risk of ischemic coronary or cerebrovascular events associated with the use of anticonvulsants that highly induce cytochrome P450 activity compared with other agents. However, the numerical increase in cerebrovascular risk supports the possibility of a modest clinical effect in the routine care of adult patients that may increase with duration on therapy.

Table 6. IRs, RRs, and RDs for Study Outcomes in PS- and hdPS-Matched Population — Intention-to-Treat Analysis*

Follow-up	Follow-up Starts on Day 1		Follow-up Starts on Day 90	
Adjustment	1:1 PS Matching	1:1 HdPS Matching	1:1 PS Matching	1:1 HdPS Matching
N episodes	22 864†	22 190†	18 203	17 703
Ischemic Coronary‡ or Cerebrovascular§ Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	230 (18.1)	214 (17.3)	163 (16.2)	154 (15.7)
Other ACs	187 (14.6)	203 (16.2)	136 (13.3)	145 (14.5)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.24 (1.02 to 1.50)	1.07 (0.88 to 1.30)	1.21 (0.96 to 1.52)	1.08 (0.86 to 1.35)
RD‖ (95% CI)	3.54 (0.40 to 6.68)	1.16 (−2.06 to 4.38)	2.85 (−0.50 to 6.20)	1.21 (−2.22 to 4.64)
Ischemic Coronary Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	129 (10.1)	123 (9.9)	99 (9.8)	95 (9.7)
Other ACs	120 (9.3)	124 (9.9)	90 (8.8)	90 (9.0)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.09 (0.85 to 1.40)	1.01 (0.79 to 1.30)	1.11 (0.83 to 1.48)	1.07 (0.80 to 1.43)
RD (95% CI)	0.79 (−1.62 to 3.20)	0.07 (−2.39 to 2.53)	0.98 (−1.67 to 3.63)	0.67 (−2.01 to 3.35)
Ischemic Cerebrovascular Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	113 (8.8)	105 (8.5)	75 (7.4)	72 (7.3)
Other ACs	84 (6.5)	87 (6.9)	59 (5.7)	61 (6.1)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.36 (1.03 to 1.80)	1.23 (0.93 to 1.63)	1.29 (0.92 to 1.81)	1.20 (0.85 to 1.69)
RDf (95% CI)	2.34 (0.20 to 4.48)	1.57 (−0.60 to 3.74)	1.65 (−0.57 to 3.87)	1.24 (−1.03 to 3.51)

IRs indicates incidence rates; RRs, rate ratios; RDs, rate differences; PS, propensity score; hdPS, high-dimensional propensity score; ACs, anticonvulsants; CI, confidence interval.

*Intention-to-treat analysis carrying initial treatment forward to occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, end of the study period or end of 2 years, whichever came first.

†Number of successfully matched patients among initiators of highly enzyme-inducing ACs and other ACs.

‡Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, or death for ischemic heart disease.

§Ischemic stroke or ischemic cerebrovascular death.

‖Rate differences are per 1000 person-years.

Table 7. IRs, RRs, and RDs for Study Outcomes in PS- and hdPS-Matched Population — As-Treated Analysis With 90-Day Extension*

Follow-up	Follow-up Starts on Day 1		Follow-up Starts on Day 90	
Adjustment	1:1 PS Matching	1:1 HdPS Matching	1:1 PS Matching	1:1 HdPS Matching
N episodes	22 864†	22 190†	19 373	18 809
Ischemic Coronary‡ or Cerebrovascular§ Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	116 (22.0)	105 (20.4)	51 (18.7)	46 (17.3)
Other ACs	97 (18.6)	102 (20.0)	47 (18.0)	45 (17.5)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.19 (0.91 to 1.56)	1.02 (0.78 to 1.34)	1.04 (0.70 to 1.55)	0.99 (0.66 to 1.49)
RD‖ (95% CI)	3.44 (−2.01 to 8.89)	0.42 (−5.09 to 5.93)	0.79 (−6.47 to 8.05)	−0.24 (−7.39 to 6.91)
Ischemic Coronary Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	57 (10.8)	54 (10.5)	27 (9.9)	26 (9.7)
Other ACs	59 (11.3)	64 (12.5)	29 (11.1)	30 (11.6)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	0.96 (0.67 to 1.38)	0.84 (0.58 to 1.21)	0.89 (0.53 to 1.50)	0.83 (0.49 to 1.40)
RD (95% CI)	−0.50 (−4.51 to 3.51)	−2.06 (−6.21 to 2.09)	−1.19 (−6.67 to 4.29)	−1.92 (−7.51 to 3.67)
Ischemic Cerebrovascular Events				
No. of events (IRs per 1000 person-years)				
Highly enzyme-inducing ACs	63 (11.9)	56 (10.9)	27 (9.9)	24 (9.0)
Other ACs	43 (8.2)	41 (8.0)	19 (7.2)	16 (6.2)
Highly enzyme-inducing ACs vs.				
Other ACs	Ref.	Ref.	Ref.	Ref.
RR (95% CI)	1.45 (0.98 to 2.14)	1.36 (0.91 to 2.03)	1.37 (0.76 to 2.46)	1.45 (0.77 to 2.73)
RDf (95% CI)	3.71 (−0.12 to 7.54)	2.85 (−0.91 to 6.61)	2.65 (−2.29 to 7.59)	2.78 (−1.92 to 7.48)

IRs indicates incidence rates; RRs, rate ratios RDs, rate differences; PS propensity score; hdPS, high-dimensional propensity score; ACs, anticonvulsants; CI, confidence interval.
*As-treated analysis allowing for a 90-day time extension after drug discontinuation.
†Number of successfully matched patients among initiators of highly enzyme-inducing ACs and other ACs.
‡Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, or death for ischemic heart disease.
§Ischemic stroke or ischemic cerebrovascular death.
‖Rate differences are per 1000 person-years.

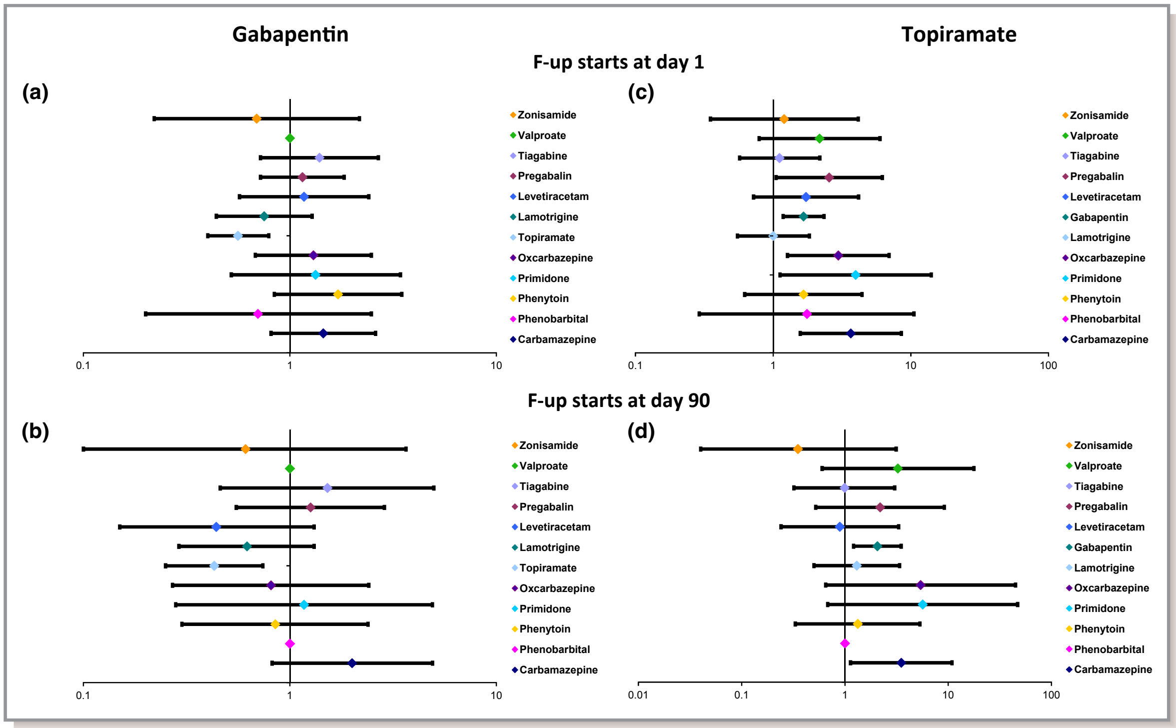


Figure 5. HdPS-matched rate ratios of ischemic coronary or cerebrovascular events[a] comparing initiators of single anticonvulsant agents against new users of gabapentin or topiramate.[b] [a]Myocardial infarction, acute coronary syndrome, cardiac revascularization procedure, death for ischemic heart disease, ischemic cerebrovascular events, ischemic stroke, or ischemic cerebrovascular death. [b]AT, as-treated analysis censoring at termination of exposure risk window, switching to another anticonvulsant agent, occurrence of a study event, death from causes not included in the study outcome, end of continuous health plan enrollment, or the end of the study period, whichever came first. hdPS indicates high-dimensional propensity score; ACs, anticonvulsants.

Disclosures

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